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Case No.: 58516US003

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	OWENS, MARY L.		
Application No.:	10/808,004	Group Art Unit:	1642
Filed:	March 24, 2004	Examiner:	B. Fetterolf
Title:	TREATMENT FOR BASAL CELL CARCINOMA		

AFFIDAVIT UNDER 37 C.F.R. § 1.131

Commissioner for Patents
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Alexandria, VA 22313-1450

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Sept. 21, 2006 — Date

Carrie M Arcand — Signed by: Carrie Arcand

Dear Sir:

STATE OF MINNESOTA)
) ss.
COUNTY OF RAMSEY)

Mary L. Owens, being duly sworn, deposes and says that:

1. I am one of the Applicants of the above-identified patent application and one of the co-inventors of the subject matter described and claimed therein.

2. Prior to September 2002, the invention as described and claimed in the above-identified application was completed in this country, the United States of America, as evidenced by the following:

a. Prior to September 2002, I contributed to the development of the Clinical Trial Protocol for Study 1305-IMIQ, attached as Exhibit I, in which a treatment regimen as described and claimed in the above-identified application is described, for example, in section 6.5.3.

b. Prior to September 2002, I reviewed the Final Report of Study 1305-IMIQ, attached as Exhibit II, and appreciated the efficacy and safety of the treatment regimen described and claimed in the above-identified application.

Further Affiant Saith Not.

Mary L. Owens MD

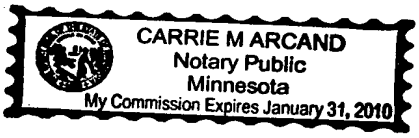
Mary L. Owens, MD

Subscribed and sworn to before me

this 15th day of September 2006

Carrie M Arcand

Notary Public



3M Pharmaceuticals
3M Center, Building 270-3A-01
St. Paul, MN 55144
20 October 1998 - Final Protocol Incorporating Changes from Amendment II

Clinical Trial Protocol
Imiquimod 5% Cream
Study 1305-IMIQ
(Descriptor IMIQ-TP-XX-CM-97-US-M)

A 12-Week Dose Optimization Trial Evaluating Imiquimod 5% and Vehicle Cream for the Treatment of Superficial Basal Cell Carcinoma

Phase II
Revised Final Protocol Incorporating Amendment II

Product:
Topical Imiquimod 5% cream

Investigator:
Multicenter

Accepted for 3M Pharmaceuticals by:

Mary L. Owens MD — 23 Oct 98

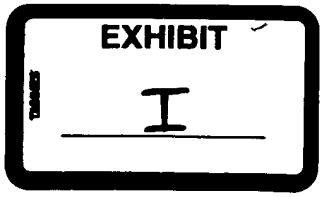
Mary L. Owens, MD — Date
Director, Clinical Research
US and International Therapeutic Head, Immunotherapeutics

Investigator Agreement: I have read the attached protocol, and agree to conduct the trial as outlined herein and according to Good Clinical Practice.

_____ — _____

Investigator Name — Date
Investigator Institution

20 October 1998



PROTOCOL ABSTRACT

[1 of 2 pages]

Project: Topical Imiquimod

Protocol ID #: 1305-IMIQ

Title: A 12-Week Dose Optimization Trial Evaluating Imiquimod 5% and Vehicle Cream for the Treatment of Superficial Basal Cell Carcinoma

Investigators: Multi-center

Monitoring: As assigned, by 3M Pharmaceuticals and Arrow Research

Clinical Phase: II

Rationale: Basal cell carcinoma (BCC) is the most common skin cancer in the United States. Pilot trials are currently underway to evaluate topical imiquimod cream for the treatment of superficial and nodular BCC. The preliminary results from these small trials indicate that imiquimod may be efficacious for these types of BCC. This trial is designed to evaluate the safety of three dosing regimens for 12 weeks of treatment, and the efficacy of imiquimod in the total clearance of superficial BCC.

Objective: To establish the optimal dosing regimen for safe and efficacious use of topical imiquimod 5% cream in the treatment of superficial basal cell carcinoma.

Study Design: Randomized, double-blind, vehicle-controlled, multi-center

Treatment: Patients will apply imiquimod 5% cream or vehicle cream topically three times per week, five times per week, or daily for 12 weeks. All patients will return to the clinic at specified intervals for assessments of efficacy and safety.

Population: Male and female patients with biopsy-confirmed superficial basal cell carcinoma (24 patients/arm; 3:1 randomization of active:vehicle) will be enrolled at approximately 10 trial sites in the United States, so that 72 evaluable patients complete the trial.

PROTOCOL ABSTRACT

[2 of 2 pages]

Evaluations: The efficacy of imiquimod 5% cream in the treatment of superficial basal cell carcinoma will be assessed by the following:

1. visual inspection
2. photography
3. post-treatment excision of target tumor area, with histological examination

The safety of imiquimod 5% cream will also be assessed:

1. review of local skin reactions at the target tumor site
2. review of adverse events and concomitant medications
3. vital signs and physical exams
4. clinical laboratory tests

Visit Procedures:

Procedure	Prestudy (-2 to -4 weeks)	Initiation	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12 (End)	6 Wks Post
Patient informed consent	X									
Inclusion/exclusion criteria	X	X								
Medical history	X	X								
History of drug therapy	X	X								
Basal cell carcinoma history	X									
Physical exam	X								X	
Vital signs	X	X	X	X	X	X	X	X	X	
Clinical laboratory tests	X								X	
Pregnancy test[a]	X	X				X			X	
Target tumor measurement	X	X								X
Target tumor photographs	X	X	X	X	X	X	X	X	X	X
Biopsy of target tumor[b]	X									
Drug application instruction		X	X							X
Drug dispensing		X		X	X	X	X	X		
Excision of target tumor area[c]										X
Drug dosing compliance			X	X	X	X	X	X	X	
Local skin reaction assessment		X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X	X
Concomitant medications			X	X	X	X	X	X	X	X
Patient status form (CRF)										X

a: Required for females of child-bearing potential (serum test at prestudy, urine test at other times)
b: Prestudy biopsy = shave biopsy, removing no more than 25% of the target tumor area
c: Excision of target tumor = post-treatment surgical excision of entire target tumor area

TABLE OF CONTENTS

[1 of 3 pages]

TABLE OF CONTENTS

[2 of 3 pages]

TABLE OF CONTENTS

[3 of 3 pages]

1. INTRODUCTION

Imiquimod cream, 5%, a drug approved in the USA in February of 1997 under the trade name Aldara™ for the topical treatment of external genital/perianal warts, is a novel immune response modifier which induces interferon production by monocytes/macrophages. Imiquimod has been shown to induce immunologic activity in human papillomavirus (HPV) -infected human skin.[1] In a clinical trial of anogenital wart patients comparing imiquimod cream to vehicle cream, imiquimod treatment stimulated significant increases in mRNA for IFN (interferon) -α, 2′5′-AS (2′5′-oligoadenylate synthetase) and IFN-γ. Increases in mRNA for CD4, CD8 and TNF (tissal necrosis factor) -α were also observed, suggesting activation of a T-helper type-1 cell-mediated response.[1]

Basal cell carcinoma (BCC) is the most common skin cancer in the United States, with approximately 1 million new cases annually, and with increasing incidence observed in the past several years in the U.S. and other parts of the world.[2,3] Basal cell carcinomas can be located on the head and neck, trunk, upper limbs or lower limbs. There are several histological basal cell carcinoma subtypes, with significant differences in site distribution and clinical outcome between subtypes. While nodular BCC is the dominant subtype for all anatomical sites, superficial BCCs are commonly seen on the trunk and limbs and are observed in patients at an earlier age.[4] Surgical excision and currettage-electrodessication are the most common treatments for primary, nonaggressive basal cell carcinomas. While these procedures are effective and have low recurrence rates when used to treat primary BCCs on low-risk anatomical sites (neck, trunk and extremities),[5,6] they are labor-intensive and expensive, and can be painful. Intralesional interferon has been shown to be effective in the treatment of basal cell carcinoma, but this therapy requires frequent clinic visits to administer injections and has a high frequency of associated flu-like side effects.[7]

Imiquimod has a unique mechanism of action, and because it is patient-applied, imiquimod 5% cream may be a more convenient and well-tolerated treatment for basal cell carcinoma than current treatments.

Additional information on imiquimod may be found in the Topical Imiquimod Investigator's Brochure.

2. RATIONALE AND TRIAL OBJECTIVE

Two pilot trials are currently being conducted to evaluate imiquimod 5% cream for the treatment of superficial and nodular basal cell carcinomas. The objective of this Phase II trial is to establish a safe and efficacious treatment regimen using imiquimod 5% cream for the treatment of primary, nonaggressive, superficial basal cell carcinoma. This trial is designed to assess the safety and efficacy of three dosing regimens with a 12-week duration of treatment. The dosing regimens were selected based on the preliminary data from the two pilot trials.

3. TRIAL SUMMARY

This is a Phase II, vehicle-controlled, double-blind, multi-center trial to be conducted in male and female patients with basal cell carcinoma. The patient population in this trial will be limited to patients with superficial BCC of limited size and with nonaggressive growth patterns, located in anatomic sites generally considered to be of low- or middle-risk for development of aggressive tumors (neck, trunk, limbs; forehead, pre- and post-auricular, and malar areas). One typical, primary superficial basal cell carcinoma with visible margins, suitable for surgical excision, will be chosen for treatment for each patient.

Patients will be randomized to one of three dosing regimens, with 24 patients per regimen. Within each treatment group, randomization will be 3:1 with 18 patients receiving imiquimod 5% cream and 6 patients receiving vehicle cream.

Patients will apply imiquimod 5% or vehicle cream three times per week, five times per week, or daily until 12 weeks of treatment are completed.

Six weeks following completion of treatment, patients will have the entire target tumor area surgically excised and histopathologically examined for evidence of residual tumor. A patient will be considered a complete responder if there is no histological evidence of cancer in the excisional sample.

To assess safety and efficacy, patients will be instructed to return to the clinic for designated visits for tumor evaluations, local skin reaction assessments, vital sign measurements and adverse events and concomitant medication documentation.

4. PATIENT SELECTION

4.1 NUMBER OF PATIENTS REQUIRED

Investigators at 10 sites will enroll a total of approximately 120 male and female patients with superficial basal cell carcinoma, so that at least 72 patients complete all trial procedures. Each site will be expected to enroll approximately 12 patients. If a site is unable to enroll 12 patients, another site may be asked to enroll more patients or additional sites will be added to meet the total enrollment goal of 72 evaluable patients. Any single site will be allowed to enroll a maximum of 24 patients.

4.2 INCLUSION CRITERIA

Patients may be enrolled in the trial if they answer "yes" to all of the following questions (inclusion criteria):

1) Is this patient able to understand and willing to give written informed consent?
2) Is this patient 18 years of age or older?
3) If female, is the patient neither pregnant nor lactating (currently or within past 3 months)?
   - Patients are considered to be of childbearing potential unless the uterus or both ovaries have been removed or they are 3 or more years post-menopausal. If female and of childbearing potential, the patient must have a negative serum pregnancy test result at the prestudy visit and a negative urine pregnancy test at initiation before drug is dispensed.
   - Females of childbearing potential must use an approved and effective method of contraception as deemed by the investigator.

- Patients who become pregnant during treatment must inform the investigator of their pregnancy, be withdrawn from the trial, and agree to provide follow-up information at delivery.

4) Is this patient willing and able to participate in the trial as an outpatient, making frequent visits to the clinic during the treatment and follow-up periods and comply with trial requirements, including the following?
   - a prestudy confirmatory biopsy between 2 and 4 weeks before beginning study drug treatment (this biopsy will remove no more than 25% of the target tumor)
   - 11 potential visits during the treatment and follow up periods
   - a post-treatment surgical excision of the entire tumor area 6 weeks following completion of treatment with study drug
   - post-treatment excisional follow-up visits until the area is healed
   - urine sampling at prestudy initiation, week 6, and end of treatment
   - blood sampling at prestudy and end-of-treatment

5) Does this patient have at least one basal cell carcinoma (target tumor) which meets the following criteria (see section 6.2.1.3 for target tumor biopsy procedures and histological definition)?
   - a primary tumor (not recurrent, not previously treated)
   - non-infected
   - located on the limbs (hands and feet excluded), trunk (anogenital area excluded), neck, or head (high-risk areas, within 1 cm of the hairline, eyes, nose, mouth, or ears excluded)
   - minimum tumor area of 0.5 cm^2 and maximum area of 2.0 cm^2
   - superficial subtype, with circumscribed growth pattern
   - not micronodular, morpheaform, aggressive, or infiltrative
   - macroscopically consistent with superficial BCC

- suitable for treatment with surgical excision
- visible and within reach of patient

4.3 EXCLUSION CRITERIA

Patients must answer "no" to all of the following questions (exclusion criteria) to be enrolled in the trial:

1) Has this patient received previous treatment with imiquimod?
2) Does this patient share a household with anyone currently being treated with imiquimod?
3) Does this patient have a current alcohol or chemical dependency as assessed by the investigator?
4) Has this patient had any previous tumor-specific therapy to the target tumor?
5) Does this patient have evidence of clinically-significant cardiovascular (NYHA Class 3), or immunosuppressive, hematologic, hepatic, neurologic, renal, endocrine, collagen-vascular or gastrointestinal abnormalities or diseases? Patients with clinically stable, controlled hypertension, diabetes mellitus type II, osteoarthritis, or other diseases may be allowed to enter the trial at the discretion of the investigator and the sponsor.
6) Does this patient have a history of allergy to any components in the cream formulation?
7) Has this patient received any of the following treatments within 4 weeks prior to treatment initiation:
   - Interferon
   - Interferon inducer
   - Immunomodulators or immunosuppressive drugs
   - Oral corticosteroids

- Inhaled corticosteroids (>1200 µg/day)
- Cytotoxic drugs
- Investigational drugs
- Drugs known to have major organ toxicity

8) Does this patient have a (non-target) basal cell carcinoma or any other skin condition requiring immediate therapy within 5 cm (~2 in.) of the target tumor?

9) Does this patient have any dermatological conditions at the target basal cell carcinoma site that would interfere with local assessments?

5. INFORMED CONSENT

Prior to entering the trial, the investigator (or his/her designated sub-investigator) will explain to each patient or his/her legal representative the nature of the trial, its purpose, procedures, expected duration, and the benefits and risks involved in trial participation. Each patient will be given the opportunity to ask questions and will be informed of his/her right to withdraw from the trial at any time without prejudice. After this explanation and before any trial-specific procedures have been performed, the patient or his/her legal representative will voluntarily sign and date an informed consent statement in the presence of a witness (investigator or designated sub-investigator) who will verify by dated signature that consent was appropriately provided. See Appendix I for Required Elements of Informed Consent (and Attachment A, Addendum for Women of Childbearing Potential).

6. TRIAL METHODOLOGY

The trial methodology section includes required prestudy procedures, procedures to be performed during the treatment period, safety evaluations, management of intercurrent disease and concomitant medication use, patient randomization and trial drug dosing procedures. A table of all trial procedures is presented in the Protocol Abstract. A Case Report Form (CRF) with instructions for completion is provided for each patient, and all pertinent pages must be completed each time the patient visits the clinic for trial procedures.

6.1 PROCEDURES

6.1.1 Prestudy Screening Visit

The objective of this visit is to identify patients who meet the stated inclusion and exclusion criteria and who are willing and able to participate in the trial. The following prestudy information and procedures must be obtained from or performed on each patient at least 2 weeks before, but not more than 1 month prior to the treatment initiation visit.

1) Signed and dated patient written informed consent obtained prior to performing trial-specific procedures.
2) Screening number assignment beginning with 901.
3) Inclusion and exclusion checklist review.
4) Medical history, including BCC history.
5) History of drug therapy received or discontinued during the 4-week period prior to the initiation visit.
6) **Evaluate the target BCC:**
   - visually identify target tumor

- measure tumor, and enter dimensions in CRF
- photograph tumor, with ruler visible in photographic field
- perform a shave biopsy, removing not more than 25% of target tumor

7) Physical examination, including vital sign measurements (sitting blood pressure, pulse, respiration and body temperature).
8) Clinical laboratory tests:
   - hematology
   - serum chemistry
   - urinalysis
   - serum pregnancy test for females of childbearing potential

6.1.2 Treatment Initiation Visit

The objective of this visit is to ensure that patients who will enter the trial continue to meet all inclusion and exclusion criteria and to perform baseline evaluations of the target basal cell tumor. This treatment initiation visit should occur **at least 14 days and not more than 1 month after the target tumor biopsy**. The following procedures should be completed at this visit:

1) Inclusion and exclusion checklist reviewed.
2) History of drug therapy review and update. Any changes in medication since the prestudy visit should be recorded on the History of Drug Therapy form.
3) Medical history review and update.
4) Vital sign measurements obtained (sitting blood pressure, pulse, respiration rate and body temperature).
5) Target tumor evaluation:
   - measure tumor, and enter dimensions in CRF

- create a template to use throughout trial, mapping locations and margins of target tumor, and visible reference marks on the adjacent skin
- photograph tumor, with ruler visible in photographic field

6) Baseline local skin reaction assessment—prestudy biopsy wound should be healed before treatment begins.
7) Urine pregnancy test for women of childbearing potential. Result must be negative before patient may receive study drug.
8) Sequential study number assigned to the patient.
9) Study cream dispensed in sequential order and recorded on the Drug Inventory Log Sheets.
10) Patient instructed on the proper application and removal of study cream.
11) Patient demonstration of drug application technique, using vehicle cream.
12) Patient diary provided and explained.

6.1.3 Interval Visits

During the 12-week treatment period, patients will be seen for interval visits at the end of weeks 1, 2, 4, 6, 8, and 10. Clinic visits should be scheduled on the same day each week. If this is not possible in a given week, the trial site personnel should attempt to get the patient back on schedule for the next clinic visit.

At the week 1 visit, each patient should demonstrate to the trial staff how he/she is applying trial drug and recording the application. If a patient is not following the application, removal, or diary completion instructions, he/she should be reinstructed on proper application procedures at this visit. Application demonstrations should be made at subsequent visits until the patient shows competence in trial drug application.

The objectives of these visits are to provide a systematic and objective evaluation of the target tumor and to monitor patient safety while ensuring continued compliance with trial procedures. Procedures and evaluations at each of these visits include the following:

1) Vital sign measurements (sitting blood pressure, pulse, respiration rate and body temperature).
2) Concomitant medications review.
3) Adverse events review.
4) Target tumor evaluation: photography of target tumor, with ruler visible in field.
5) Local skin reaction assessment.
6) Test drug dosing diary review, to monitor dosing compliance.
7) Urine pregnancy tests for female patients of childbearing potential at week 6.
8) Used cream packets collected and new packets dispensed (every 2 weeks, with the exception of week 1).

6.1.4 End-of-Treatment Visit

End-of-treatment procedures will be performed when the patient has completed the full 12 weeks of treatment or at the time of premature discontinuation from the trial. In addition to evaluations listed for each interval visit, the end-of-treatment procedures listed below will be completed:

1) Clinical laboratory tests:
   - hematology
   - chemistry
   - urinalysis
   - urine pregnancy test for females of childbearing potential

2) Physical examination, including vital sign measurements (sitting blood pressure, pulse, respiration rate and body temperature).
3) Collection of all used and unused packets of trial cream from the patient including "Emergency Use" supplies.

6.1.5 6-Week Post-treatment Excisional Surgery Visit

Six weeks following completion of treatment with the study cream, all patients will have the entire target tumor area surgically excised and sent to the central dermatopathology laboratory for sectioning and histological examination for evidence of remaining tumor. Any patient who discontinued treatment prematurely should be encouraged to return to the clinic for the excision. Only patients who have no histological evidence of basal cell carcinoma will be considered complete responders.

Procedures and evaluations to be performed at this visit include the following:

1) Target tumor evaluation prior to the excisional surgery:
   - measurement of target tumor, if clinically evident
   - photography of target tumor site, with ruler visible in field
2) Local skin reaction assessment.
3) Review and record adverse events and concomitant medications.
4) Surgically excise the entire target tumor area.

6.1.6 Excisional Surgery Follow-Up Visits

Patients should return to the clinic every 2 weeks following the surgical excision until it is determined by the investigator that the area has sufficiently healed (eg, wound closed,

stitches removed). The "Excision Follow-Up" CRF pages should be completed for these follow-up visits. Complete the patient status CRF page.

6.2 METHODS OF ASSESSMENT

6.2.1 **Target Tumor Assessment**

6.2.1.1 Measurement of Target Tumor

At the treatment initiation visit, the baseline area of the target tumor will be determined by measuring the two largest perpendicular dimensions of the target tumor.

If target tumor is clinically evident at the 6-week post-treatment visit, prior to the excisional surgery, the perpendicular dimensions of the tumor will be measured.

6.2.1.2 Photographs of Target Tumor

Photographs of the target tumor will aid in tracking the changes in the target tumor as well as documenting any local skin reactions. Photographs of the target tumor should be taken at the prestudy visit **prior** to the initial biopsy, the treatment initiation visit, each treatment visit, the 6-week excisional surgery visit **prior** to excision of the target tumor area, and at the excision follow-up visits.

Provided rulers which include the study and site number, patient number and initials, visit date, and week of the visit, must be held in place near the target tumor and clearly visible in the photographic field. Two copies of each photograph are required: one for 3M Pharmaceuticals (print) and one for the investigator's records. Acceptable forms of photography include Polaroid or 35-mm prints or slides, and film should be promptly

processed so that photographs can be reviewed and filed in the patient's CRF before the next clinic visit. If the investigative site does not have a suitable camera and lens for taking close-up photographs of the skin, one will be loaned to the investigator by 3M Pharmaceuticals for the duration of the study.

6.2.1.3 Target Tumor Biopsy/Excision

Prestudy biopsies and post-treatment excisional specimens will be sent to the central dermatopathology laboratory where they will be sectioned and histologically examined for tumor; the pathology reports will be sent to the investigator for review.

Prestudy Target Tumor Biopsy

Between 2 and 4 weeks prior to the initiation visit, up to four punch or deep shave biopsies will be performed to confirm histologically that the patient has a tumor that is a superficial basal cell carcinoma appropriate for treatment. Each biopsy will be given a unique identifier letter (A, B, C, or D) which will be entered into the case report form (CRF). Only one biopsy-confirmed superficial basal cell carcinoma on each patient will be selected as the target tumor. The biopsies will remove no more than 25% of the tumor area and will penetrate into the reticular dermis. The biopsies should extend through the entire depth of the tumor. All biopsy specimens will be sent to the primary dermatopathology laboratory for processing and evaluation. A preliminary dermatopathology report will be sent to the investigator (by courier or fax) within 2 working days of the receipt of prestudy biopsy specimens. Slides from all biopsies will be forwarded to a second dermatopathology laboratory. The final dermatopathology report will be sent to the investigator (by courier or fax) within 10 working days of the receipt of a prestudy biopsy specimen.

The following histopathological features must be observed microscopically for the tumor to be suitable for treatment in this trial:

Basal cell carcinoma, superficial type: Sections show one or more proliferations of basaloid epithelial cells extending from the under-surface of the epidermis into the papillary dermis, which exhibit peripheral palisading, mitotic figures, necrosis, and clefting from the surrounding fibromucinous stroma. The tumor is confined in the biopsy to the superficial reticular and papillary dermis.

Post-treatment Target Tumor Excision

Six weeks following completion of treatment with the study cream, patients will have the entire target tumor area surgically excised, including a 3-4 mm margin around the tumor. The excised specimen will be processed according to the instructions below and the sections and step-sections will be histologically examined at the central dermatopathology laboratory for evidence of any residual BCC and to ensure that the excisional margins are free of tumor. A second dermatopathologist will also examine all slides. The final dermatopathology report will be sent to the investigator (by courier or fax) within 10 working days of the receipt of a post-treatment excisional specimen.

Processing of Excised Specimen

To ensure that each excised specimen is thoroughly examined, the following instructions will be followed by the central facility (Mayo Clinic/Mayo Medical Laboratories, Rochester, MN) for processing:

- Elliptical specimens should have surgical margins inked for left and right lateral margins, tips, and deep margins (4 colors).

- Blocks will be embedded properly in the required number to adequately section the tissue specimen, which will vary with the size of the ellipse.
- The entire specimen will be breadloafed into sections not more than 3 mm thick. The center (as marked by the surgeon with a small cut or stitch) of each specimen will be sequentially sectioned in 1-mm increments for the first 3 mm in either direction from the center. The remainder of the specimen (through the tips) will be sectioned every 3 mm.
- At least six (6) and up to twenty (20) or more sections will be examined per case, depending on the size of the ellipse that was excised. Sections will be sequentially numbered for identification.
- Blocks should be thoroughly effaced to ensure adequate histological review of the margins.

All slides and any remaining tissue blocks (prestudy biopsy and excisional specimen) from each patient will be retained in storage as study records.

6.2.2 Safety Evaluations

6.2.2.1 Laboratory Tests

Routine Clinical Laboratory Tests

All patients will have complete clinical laboratory tests performed at the prestudy and end-of-treatment (week 12) visits to include the following profiles for hematology, chemistry, and urinalysis:

Hematology	
Hemoglobin	White blood cell count (WBC)
Hematocrit	with differential
Red blood cell count (RBC)	Platelet count

Chemistry

Glucose	Potassium
BUN (urea nitrogen)	Sodium
Creatinine	Calcium
Total bilirubin	Chloride
AST (SGOT)	Total protein
ALT (SGPT)	Albumin
Lactate dehydrogenase (LDH)	Phosphorus
Alkaline phosphatase (ALP)	Cholesterol

Urinalysis

Color/appearance	Glucose
pH	Ketones
Specific gravity	Microscopic examination
Protein	

For Female Patients

Females of childbearing potential will undergo a serum pregnancy test at prestudy. Results must be negative for enrollment in the study. At the treatment initiation visit, a urine pregnancy test will be performed to confirm negative results before treatment with study cream can begin.

Urine pregnancy tests will be repeated at week 6, and at end of treatment. If at any time a pregnancy test result is positive, the patient must be discontinued from the trial. Patients are considered to be of childbearing potential unless the uterus or both ovaries have been removed or they are at least 3 years post-menopausal.

Blood and urinalysis specimens will be sent to and analyzed by:

Covance Central Laboratory

8211 SciCor Drive, Indianapolis, IN 46214-2985

Investigator Services Telephone: 800-327-7270

Procedures regarding the acquisition of these specimens will be supplied to the investigator by Covance prior to the initiation of the trial. A report of all laboratory values will be sent to the investigator and the sponsor for review and analysis.

6.2.2.2 Local Skin Reaction Assessment

At each clinic visit after the prestudy visit, local skin reactions will be evaluated at the tumor site. Erythema, edema, induration, vesicles, erosion, ulceration, excoriation/flaking and scabbing will be visually assessed by a member of the clinical staff during the clinic visits using the following rating scale and recording the most severe reaction noted for each category above:

0 = none

1 = mild

2 = moderate

3 = severe

In addition, patients will be asked if they observed local symptoms (without prompting the patients for specific skin reaction terms) at the target site during the treatment period since the last clinic visit that were different from those apparent during the current visit. If a patient did observe different reactions during the interval, the site personnel will translate the patient's report of reaction(s) into the CRF using any appropriate categories listed above, and the same scale will be used to describe the severity of the reaction(s) observed by the patient.

0 = none: no reaction recalled by the patient

1 = mild: visible reaction without discomfort, or with minimal discomfort that does not disrupt daily activity

2 = **moderate:** visible reaction with considerable discomfort, but not disruptive of daily activity

3 = **severe:** visible reaction that substantially interferes with daily activity

A comment stating when the reaction occurred (eg, date and time, or time in relation to dose application) will also be entered on the CRF page if such information was noted by patient.

6.3 INTERCURRENT DISEASE TREATMENT AND CONCOMITANT MEDICATIONS

6.3.1 **Intercurrent Disease Treatment**

Patients who enter the trial with more than one basal cell carcinoma tumor or patients developing additional tumors during the trial may receive conventional forms of treatment for the non-target tumors during the treatment and follow-up periods if the following criteria are met:

- the tumor(s) are sufficiently distal from the target tumor to prevent interference with the target tumor (at least 5 cm),
- the treatment is not listed in the Exclusion Criteria for this study, and
- the treatment will not affect the target tumor.

Each patient may treat only the single target tumor with imiquimod while participating in this study.

6.3.2 Concomitant Medications

Drug treatment for local skin reactions is limited to oral acetaminophen. Patients may not receive any treatment or medication that is listed in the exclusion criteria, Section 4.3.

The investigator will query patients at each clinic visit to determine if concomitant medications were taken. Any medications taken by the patient during the course of the trial for treatment of an adverse event or intercurrent illness will be recorded on the Record of Concomitant Medication page in the CRF.

6.4 IMIQUIMOD APPLICATION PROCEDURES

In this trial, patients will apply imiquimod 5% or vehicle cream three times per week, five times per week, or daily for 12 weeks. Study drug will be provided in single-use packets, with patients receiving a box containing enough packets of cream for two weeks' use at each interval clinic visit (except week 1).

6.4.1 Patient Instruction

During the treatment initiation visit, the trial staff will demonstrate to the patient the proper technique for applying the cream. Patients will also be instructed as to how much cream should be applied with each dose, based on the size (largest diameter) of the target tumor, using the following guidelines:

Target Tumor Diameter	Size of Cream Droplet to be Used (diameter)	Approximate Amount of Cream to be Used
0.5 - 1.0 cm	○ (4 mm)	10 mg
1.0 – 1.5 cm	○ (5 mm)	25 mg
1.5 – 2.0 cm	○ (7 mm)	40 mg

The patient will demonstrate the application technique using vehicle cream. In addition, patients will receive written instructions on the application and removal of the cream prior to leaving the clinic. An example of these instructions is contained in Appendix II. Diaries will be provided to the patient for recording dates and times of study cream application and removal.

6.4.2 Study Drug Application and Removal

Trial cream should be applied prior to normal sleeping hours. Instructions to the patient will include the need for washing hands with mild soap and water before and after application of imiquimod cream. Patients will also be instructed that the target tumor should be gently cleaned and dried before each cream application. The patient should use the fingertip to apply the cream from the packet, using the amount of cream instructed, and rub the cream into the entire tumor area and the area approximately 1 cm (~1/3 inch) around the target tumor until the cream vanishes. The treatment site should not be occluded with tape or bandages.

Patients will remove the cream with mild soap and water after it has been on the skin for at least 8 hours and prior to applying the next dose of cream. Patients are to record the exact time of cream removal in the patient diary. Patients should not bathe, shower, or swim for at least 8 hours after each application of cream.

At the week 1 visit, the patient should demonstrate to the investigator how he/she is applying and removing study drug. If the patient is not following the application and removal instructions, the investigator should reinstruct the patient on proper application procedures and follow-up on patient technique at subsequent interval visits.

6.4.3 Frequency of Application

Patients should be instructed to apply the cream according to the trial drug regimen to which they are assigned. Each dose should remain on the skin for at least 8 hours. If a dose of cream is washed off before 8 hours has elapsed, the reason for premature removal should be stated in the diary next to the removal time entry.

Three Times per Week Dosing

Cream should be applied three times per week on the same three days of each week (every other day followed by 2 days without treatment), prior to normal sleeping hours. For example, cream could be applied every Monday, Wednesday, and Friday; or every Tuesday, Thursday, and Saturday.

Five Times per Week Dosing

Cream should be applied five times per week on the same consecutive five days of each week (five days in a row followed by 2 days without treatment), prior to normal sleeping hours. For example, cream should be applied every Monday, Tuesday, Wednesday, Thursday, and Friday followed by Saturday and Sunday without treatment.

Daily Dosing

Cream should be applied once on each day of the week, prior to normal sleeping hours.

6.4.4 Documentation of Study Drug Dosing

The patient is responsible for maintaining a diary throughout the course of treatment to document study drug dosing. At the treatment initiation visit, the investigator and study staff should describe the use of the diary and the importance of completion; and instruct the patient to bring the diary to each clinic visit.

With each dose of study drug, the patient should record the dates and exact times of application and removal. At each interval visit, the investigator or trial coordinator will transcribe the data recorded in the patient diaries to the patient's case report form.

In addition to transcribing the data, the study personnel should carefully review the diary entries to make sure the patient is applying the cream as instructed and maintaining the dosing schedule by applying the cream on the same days each week.

If the patient is not following the dosing schedule, he/she must be reminded of the schedule previously established and the need to maintain it. If the patient continues to be noncompliant he/she must be discontinued from the trial. Significant deviations from the dosing regimen, defined as cream application for less than 8 hours must be noted by the clinical staff on the case report form, with an explanation for the short duration of application.

6.4.5 Missed Doses

Patients are allowed to miss doses, however patients should be encouraged to follow their assigned dosing regimen and should not be informed that they can miss any doses. Patients who consistently miss doses and are not on a rest period should be informed that

their continued noncompliance may result in discontinuation from the trial. The treatment period will not be extended beyond 12 weeks due to missed doses or rest periods.

6.4.6 Rest Periods

Rest periods of up to 7 days may be prescribed if the patient is unable to apply doses due to local skin reactions or treatment site adverse events. Patients taking a 7-day rest period will be required to apply a minimum of 3 doses before another rest period can be taken. As soon as the local skin reaction or adverse event has been assessed by the investigator and s(he) has determined that recovery of the area or the adverse event is sufficient, the patient will be instructed to resume dosing. Any rest periods will be considered part of the 12-week treatment period. If a patient needs to take more than two rest periods (a total of 14 days rest), s(he) will be discontinued from the study.

6.5 TRIAL ENDPOINTS

Following treatment initiation, each patient's trial participation will end when one of the following occurs:

1) Patient has completed all study procedures including
   - 12 full weeks of treatment (measured from treatment initiation),
   - 6-week post-treatment excisional surgery, and
   - excisional surgery follow-up visit(s);
2) Patient discontinues study participation prior to completion of all study procedures.

6.6 PATIENT COMMITMENT TO TRIAL

For each patient, the trial is expected to last a minimum of 22 weeks and a maximum of 24 weeks. Each patient will undergo a prestudy shave biopsy of his/her target tumor as well as a post-treatment excisional surgery. The total amount of blood drawn will be up to approximately 25 mL, or approximately 12 mL at each of 2 sampling times during the trial; urine specimens will be collected at up to four times during the trial.

6.7 PATIENT WITHDRAWAL AND DISCONTINUATION

Patients may withdraw themselves or have the investigator withdraw them from the trial at any time without prejudice to their future medical care. Any patient who does not comply with the inclusion/exclusion criteria listed in sections 4.2 and 4.3 of the protocol will be withdrawn from further participation in the trial. Patients may be discontinued if the investigator has determined that the patient has experienced local skin reactions of severe intensity or duration to warrant discontinuation. If a patient discontinues due to a local skin reaction or an adverse event, the patient will be followed until the adverse event resolved to the investigator's and sponsor's satisfaction.

Any patient who receives study drug must complete the appropriate end-of-treatment procedures, and all patients will be asked to return six weeks after conclusion of study drug treatment for excision of the target tumor area; the investigator must complete the end-of-study patient status form in the CRF for every patient enrolled in the trial.

Patients who discontinue prematurely from treatment or during follow-up will not be replaced, and sites are encouraged to carefully select patients that would be likely to complete all study procedures.

7. REPORTING OF ADVERSE EVENTS

Local skin reactions such as erythema, edema, vesicles, erosion, ulceration, excoriation, and scabbing, and treatment site adverse events including pain, burning and itching have been reported at the application site and at remote sites with the use of imiquimod 5% cream in patients with basal cell carcinoma.[8] Other adverse events, such as fever, chills, headache, fatigue, nausea and myalgia, have been associated with oral administration of imiquimod in single doses of 200 mg or greater, and are thought to be due to induction of interferon and other cytokines.[9] In a large Phase III study of imiquimod 5% cream in 311 genital warts patients, there was no difference in the incidence flu-like symptoms between imiquimod and vehicle-treated patients.[10]

The investigator must report in detail all adverse events that occur on the appropriate CRF page (local skin reactions previously described are reported separately from other adverse events). Included in the description will be the nature of the sign or symptom; the date of onset; date of resolution; the severity; the relationship to study treatment; the action taken (if any), and the outcome.

Adverse event severity will be described as mild, moderate, or severe, using the following definitions:

Mild: The patient is aware of symptoms or signs, but they cause minimal discomfort and are easily tolerated by patient.

Moderate: The symptoms or signs are sufficient to restrict but not to prevent the patient's daily activity.

Severe: The patient is unable to perform usual daily activity due to adverse event.

If any adverse event or local skin reaction is ongoing at the time of the final follow-up visit, the investigator must continue to follow the adverse event or local skin reaction until resolution or until resolved to the investigator's and sponsor's satisfaction.

In addition, in the event of a serious or unexpected adverse event, the investigator will **immediately** notify 3M by telephone:

Contact	Office	Home
Assigned Monitor		
Angie Ginkel, CRA	1-651-737-2045	1-651-647-9662
Aimee Couture, CRA	1-651-733-9670	1-651-714-8120
Mary L. Owens, MD	1-651-736-3638	1-651-459-0975

In the event none of the above people are available, the following emergency number is in operation at all times:

1-800-862-5888

The Institutional Review Board (IRB) must be informed if the serious or unexpected adverse event, in the opinion of 3M or the investigator, is likely to affect the safety of the patients or the conduct of the trial.

A **serious adverse event** is defined as any adverse experience or adverse drug experience that results in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly/birth defect. An event may be considered serious when, based upon appropriate medical judgment, it jeopardizes the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

A **life-threatening adverse event** is any adverse experience or adverse drug experience that places the patient, in the view of the investigator, at immediate risk of death from the event as it occurred. It does not include a reaction or experience that, had it occurred in a more serious form, might have caused death.

Requires inpatient hospitalization should be defined as hospital admission required for the treatment of an adverse event. Hospital admission for scheduled elective surgery would not be considered a serious adverse event.

An **unexpected adverse event** is any adverse drug experience, the specificity or severity of which is not consistent with the current Investigator's Brochure.

8. MATERIALS AND SUPPLIES

8.1 RANDOMIZATION

Patients will be randomized to one of three regimens listed below, with 24 patients per dosing regimen. Within each regimen, patients will be randomized to treatment with imiquimod or vehicle cream (3:1, imiquimod:vehicle):

- 3×/ week application with imiquimod 5% cream (n=18)
  3×/ week application with vehicle cream (n=6)
- 5×/ week application with imiquimod 5% cream (n=18)
  5×/ week application with vehicle cream (n=6)
- 7×/ week (daily) application with imiquimod 5% cream (n=18)
  7×/ week (daily) application with vehicle cream (n=6)

Drug supplies will be packaged and labeled by Simirex, Inc. and will be randomized according to a computer generated randomization schedule. Upon randomization, patients will be allocated a unique patient ID number in numerical sequence. 3M will supply the investigator with the randomization code for each patient in the hidden panel on the detached drug label. The code will only be broken in an emergency such as in the occurrence of a serious or unexpected adverse event. If the code for a patient is broken, the investigator must inform 3M within 24 hours. The investigator will submit a written explanation to 3M within 5 working days. The reason for breaking a patient's code must be recorded on the appropriate case report form. If for any reason the code is broken, the patient will be withdrawn from the study.

3M will not break the code until all data have been collected, quality controlled, and accepted for analysis, except in cases of emergency.

8.2 TRIAL DRUG PACKAGING

3M Pharmaceuticals, St. Paul, MN (or a packaging facility under contract with 3M Pharmaceuticals) will initially supply a sufficient number of packets for 12 patients at each of 10 sites. Additional drug supplies will be provided as needed.

3M Pharmaceuticals (or a contract facility) will prepare and supply imiquimod 5% cream (formulation U-2e) and vehicle cream in single-use packets, with patient kits packaged in boxes containing enough packets of study cream for a patient to dose for two weeks (number of packets per box will vary with assigned dosing regimen). An empty, self-sealing polyethylene bag will be provided with each patient kit for the return of used cream packets.

Additionally, four "Emergency Use" patient kits will be available for each patient. Each one will contain a 1-week supply of packets (3 to 14 packets, depending on the dosing regimen).

Vehicle cream packets will also be supplied to the site for demonstration of proper trial cream dispensing and application.

8.3 TRIAL DRUG LABELING

3M Pharmaceuticals (or a contract facility) will label all primary drug containers, patient kit boxes, and bags for return of used drug to clearly identify patient number. Labeling for the packets, patient dispensing boxes, patient packs, site shippers and self-sealing polyethylene bags is detailed on the following table.

	Packets	Patient Dispensing Boxes-Permanent Label	Patient Dispensing Boxes-Detachable Label	Patient Dispensing Boxes-Hidden Label	Return self-sealing Bag Label	Patient Pack Labels	Site Shipper Box Label	Vehicle Packets (for Demo)	Vehicle Box Labels (for Demo)
Contains 250 mg Imiquimod 5% or Vehicle Cream	X							X	
Contains (3, 6, 7, 14, 28, or 30) Packets, Each with 250 mg Imiquimod 5% or Vehicle Cream		X	X		X				X
Contains (__) Boxes, each with (3, 6, 7, 14, 28 or 30) Packets of Imiquimod 5% or Vehicle Cream						X			
Study 1305-IMIQ-(___) (site completes number on patient boxes only)	X	X	X		X	X	X	X	X
Patient Number(s)		X	X	X	X	X	X		
Week Number or "For Emergency Use Only" Week (A, B, C, or D)		X	X		X				
Date Dispensed		X	X						
Imiquimod 5% or Vehicle Cream				X					X
Lot Number				X				X	X
Use as Directed (3×, 7×, or 14× per week)		X	X						X
Store below 77°F. Avoid freezing.	X	X				X	X	X	X
Caution: New drug--Limited by US Law to Investigational Use Only	X	X	X		X	X	X	X	X
3M Pharmaceuticals, 3M Health Care, St. Paul, MN 55144-1000	X	X	X		X	X	X	X	X
Excipients		X	X						X
For Demonstration Use only									X
Vehicle contains no active ingredients									X

8.4 TRIAL DRUG DISPENSING

When enrolled, each patient will receive two "Emergency Use" boxes of packets. At each clinic visit, each patient will be given a sufficient number of packets to be used until the next interval visit (2 weeks). Patients will be instructed to return trial cream supplies, except for unopened "Emergency Use" supplies, at each visit. If patients use any materials from the "Emergency Use" supply, they should return the opened box(es) to the clinic at the next visit for replacement.

At each time trial drug is dispensed,

1) Remove the appropriate self-sealing polyethylene bag from the patient kit,
2) Write the date dispensed on the following **two** labels:
   - box containing 2-week supply of packets
   - detachable label for the patient CRF page,
3) Issue the appropriate number of diaries.

For the 5x/week dosing schedule, the drug originally packaged for the 2x/day dosing schedule will be used. The dosing instructions on the drug carton label will be changed from "Use as directed 14 times per week" to "Use as directed 5 times per week." The contents on the drug carton label will be changed from "Contents: 28 packets, Each with 250 mg" to "Contents: 10 packets, Each with 250 mg." In addition, 18 packets of cream will be removed from each two-week supply of drug when it is dispensed, so that each two-week drug supply kit will contain 10 packets of cream.

Similarly, "Emergency Use" drug labels will be changed. The dosing instructions will be changed from "Use as directed 14 times per week" to "Use as directed 5 times per week." The contents on the drug carton label will be changed from "Contents: 14 packets, Each

with 250 mg" to "Contents: 5 packets, Each with 250 mg." Nine packets of cream will be removed from each "Emergency Use" drug carton before dispensing.

All packets, both used and unused will be returned to 3M Pharmaceuticals at the completion of the trial.

8.5 FORMULATION

The U-2e formulation of the imiquimod 5% cream contains imiquimod (12.5 mg per packet), isostearic acid, benzyl alcohol, cetyl alcohol, stearyl alcohol, polysorbate 60, sorbitan monostearate, white petrolatum, glycerin, methyl paraben, propyl paraben, purified water, and xanthan gum.

The vehicle packets contain the same ingredients as the active packets with the exception of imiquimod.

The trial drug supplies should be stored below 77°F. Avoid freezing.

Additional supplies and materials required to perform this trial are listed below.
3M Pharmaceuticals will provide these supplies.

1) Patient case report forms (CRFs)
2) Patient diaries
3) Camera (if needed), film and photo sleeves
4) Labels and tongue depressors for target tumor photographs

9. DATA ANALYSIS AND STATISTICAL PROCEDURES

9.1 SAMPLE SIZE DETERMINATION

Since confirmation of efficacy is one of the goals of this trial, sample size calculations were based on the ability to detect differences in complete response rates. Eighteen patients in each of the three imiquimod dose groups and 18 patients in the combined vehicle group give this trial at least 80% power to detect a difference in complete response rates of 20% for vehicle patients vs. 80% for any of the imiquimod dose groups, assuming that each imiquimod vs. vehicle comparison is carried out at an alpha level of 0.05/3. In order to have a total of 72 patients who qualify for the evaluable-for-efficacy analysis, clinic centers will be asked to enroll a total of approximately 120 patients.

9.2 STATISTICAL PROCEDURES

The statistical analysis of this study will be completed by the Biostatistics section of the Medical Operations Department, 3M Pharmaceuticals, St. Paul, Minnesota, USA.

9.2.1 Data Sets to be Analyzed

The primary data set to be analyzed for efficacy and safety is the intent-to-treat data set. This data set includes all randomized patients who applied at least one dose of study cream and provided any on-treatment data.

An evaluable-for-efficacy data set will also be analyzed. This data set includes all patients who completed the post-treatment excisional surgery and who applied at least 60% of the doses required by the dosing schedule to which they were randomized. For example, a patient in a once-daily application group should apply a total of 84 doses

(7 doses per week for 12 weeks). For this patient to be included in the evaluable-for-efficacy data set, (s)he must apply at least 51 doses of study cream (60% of 84 = 50.4), and complete the post-treatment surgical excision.

9.2.2 Demography and Baseline Characteristics

Baseline characteristics will be examined to assess whether the patients randomized to the treatment groups were comparable prior to the initiation of treatment. Characteristics to be evaluated include age, gender, race (white vs. nonwhite), height, weight, tobacco use (current vs. never/past use) and alcohol use (current vs. never/past use).

For continuous variables, the null hypothesis is that the treatment group mean baseline values are equal versus the alternative that they are unequal will be tested using a one-way analysis of variance. For categorical variables, the null hypothesis of marginal homogeneity of the baseline characteristic (e.g., race) across treatment groups will be tested with Fisher's Exact Test.

9.2.3 Efficacy Parameters: Analyses

The goals of this study include confirmation of efficacy, the investigation of the shape of the dose-response curve, the determination of the minimum and maximum effective doses, and estimation of the ratio of efficacy to severe local skin reactions at each dose level. Therefore, the application of statistical estimation procedures, including the construction of confidence intervals and the use of graphical methods, will be emphasized.

9.2.3.1 Primary Parameter: Proportion of Patients with Complete Response

The primary efficacy variable is the proportion or rate of patients who were complete responders to treatment, defined as no histological evidence of basal cell carcinoma in the post-treatment excisional specimen of the target tumor area. The vehicle data from all the dosing groups will be pooled together to estimate the vehicle response rate. Fisher's Exact Tests will be used to compare the response rates of the imiquimod dose groups to the combined vehicle group in a pairwise manner. A Bonferroni adjustment will be made to preserve the overall alpha level at 0.05; i.e., each pairwise comparison will be carried out at an alpha level of 0.05/3.

In the intent-to-treat analysis, patients who withdraw prior to completing the post-treatment excisional surgery will be managed as "nonresponders".

Plots of the proportion of patients with complete response vs. dose level will be constructed to visually examine the data with respect to the shape of the dose-response curve. Logit and/or probit models will be used to characterize the dose-response function. Estimation of the proportion of complete responders with 95% confidence intervals at each dose level will also be completed.

A "therapeutic window" plot will be prepared, to examine the proportion of patients with complete treatment response vs. the proportion of patients with severe local skin reactions at each dose level. Visual inspection of this plot will provide information about the benefit-to-risk ratio at each dose level.

9.2.4 **Safety Parameters: Analyses**

All safety measures will be analyzed using the intent-to-treat patient population.

9.2.4.1 Adverse Events

Adverse events will be summarized by the World Health Organization's preferred terms and body systems, as modified by 3M Pharmaceuticals. The incidence of adverse events (percent of patients reporting the adverse event at least once) will be tabulated separately for each dose group. A separate analysis of incidence will be conducted including only events coded as "probably related to treatment" or "possibly related to treatment."

In addition, verbatim terms under the preferred term "application site reaction" will be grouped into "included terms" to examine in more detail the various kinds of application site reactions. For example, verbatim patient-reported terms with "itching" as part of the term will be grouped together to estimate the incidence for "itching at target site" or "itching at remote site." Included terms will distinguish between target site and remote site.

9.2.4.2 Local Skin Reactions

The scores for local skin reactions at the target site will be tabulated separately for each dose group. Separate tabulations will be constructed for assessments made by the investigator and for assessments made by the patient. Additional tables will present frequency distributions of the most severe assessments over the course of the study.

9.2.4.3 Laboratory Data

Tables showing shifts of values in and out of the normal (reference) range will be constructed separately for each dose group. In addition, all laboratory values falling outside of the normal range will be tabulated.

9.2.4.4 Vital Signs and Physical Examination Data

Patients' change from baseline for vital signs will be tabulated separately for each dose group. The vital signs obtained at the initiation visit will be used as the baseline values.

Any clinically significant changes in physical exam findings will be discussed in the study report.

9.2.4.5 Concomitant and Prestudy Medications

If the medication stop date (if present) or latest possible medication stop date occurs within 4 weeks of the study initiation date, then the medication will be included as a concomitant medication (due to possible medication carryover). If the medication start date (if present) or earliest possible medication start date occurs before the initiation date, then the medication will be included as a prestudy medication. Medications can be classified as both prestudy and concomitant medications.

If medication start or stop dates are incomplete, the following procedure will be used to estimate the earliest start date and latest stop date.

If the medication day is missing, but month and year are present, then the latest stop date is estimated to be the last day of the month. If the medication month is not the same as the treatment initiation month, then the earliest start date is estimated to be the first day of the month. If the medication month and year are the same as the treatment initiation month and year, then the earliest start date is estimated to be the day of treatment initiation.

If both the medication month and day are missing, but year is present, then the latest stop date is estimated to be the last day of the year. If the medication year is not the same as the treatment initiation year, then the earliest start date is estimated to be the first day of the year. If the medication year is the same as the treatment initiation year, the earliest start date is estimated to be the month and day of treatment initiation.

9.2.5 Statistical Software

All statistical analyses will be performed using SAS (R) Version 6.12. PROC FREQ will be used to produce the frequency distributions and the Fisher's Exact Tests. PROC UNIVARIATE will be used to generate all descriptive statistics. PROC GLM will be used to do the one-way analysis of variance.

9.2.6 Pooling Results Across Study Centers

There will not be sufficient patients enrolled at each study center to carry out a meaningful analysis of treatment-by-center interactions. However, the complete response rate data will be displayed separately by center, and any extreme or opposite results among centers will be noted and discussed.

10. FINAL TRIAL REPORT

A final trial report will be written as part of 3M's commitment to Good Clinical Practice. This report will be a record of the total trial conduct and will be subject to approval by the principal investigator, who will sign the final report; the principal investigator will be preselected by 3M Pharmaceuticals.

11. ADMINISTRATIVE PROCEDURES

11.1 INSTITUTIONAL REVIEW BOARD

This trial will only be undertaken when full approval of the protocol and patient information and consent form has been obtained from the appropriate Institutional Review Board(s) (IRB) and a copy of the final approval letter is received by 3M. The investigator will submit to 3M a copy of the approval letter or notice by the IRB approving the final copy of this protocol and informed consent form, including any suggested changes.

The approval letter or notice must contain the date of the meeting and sufficient information to identify the version of the protocol unambiguously (by name, date and number) and state that the informed consent form, and any other material submitted to them (e.g. patient information sheet, CRF, advertisement for patient recruitment, patient compensation, investigator compensation) was also reviewed and approved. If the approval letter is deficient in these references, it is acceptable for the list of documents submitted to the IRB to be filed together, attached to the approval letter.

The investigator must inform, or submit for approval to, the IRB of all relevant protocol or consent form amendments, according to local practice.

It is also necessary for the investigator to submit to 3M a list of the IRB members plus their institutional affiliations, occupations, and a means of determining gender makeup.

11.2 REGULATORY REQUIREMENTS

The protocol will be submitted to the US Food and Drug Administration Division of Dermatologic and Dental Drug Products (HFD-540) under IND 49,464.

11.3 TRIAL PERSONNEL

Prior to the start of the trial, each investigator must supply 3M with a list of the names of the clinically responsible investigator(s) of the trial and the names of other major participants in the trial (who are directly involved with procedures affecting the patient) together with their profession (e.g. medical doctor, nurse, phlebotomist, medical technologist, etc.).

11.4 PRE-TRIAL DOCUMENTATION REQUIREMENTS

Prior to shipment of trial drug, the following documents must be submitted or returned to 3M by the investigator.

1) Signed final version of this protocol including any amendments in place prior to trial starting.
2) Completed (signed and dated) FDA Form 1572.

3) Signed and dated curriculum vitae of the investigator, sub-investigator(s) and other site personnel assisting in the conduct of the trial (as listed on FDA Form 1572).
4) IRB details and letter of approval as listed in Section 11.1 of this protocol.
5) Signed and dated confidentiality agreement.
6) Signed and dated financial agreement.

11.5 COMPLETION AND RETURN OF CASE REPORT FORMS (CRFS)

All case report form entries must be made in black ink. The investigator must review all entries for completeness and correctness. When changes or corrections are made on any case report form, the investigator, co/sub-investigator, nurse or trial coordinator must draw a single line through the error then initial and date the correction as well as stating the reason for the error, except when due to a transcription error. The investigator agrees to complete and sign case report forms in a timely fashion after completion of each patient and make them available to the trial monitor for full inspection. Before acceptance, the clinical monitor will review the case report forms for completeness and adherence to the protocol. The top (white) and third (pink) copies will be submitted to 3M. The second (yellow) copy will be retained by the investigator in his/her files (see Section 11.12). NO CHANGES WILL BE MADE TO THE SECOND (YELLOW) COPY AFTER THE TOP COPY IS REMOVED. Case Report Form Inquiry (CRFI) forms will be used to make any necessary changes after the top copy of CRF has been removed.

11.6 DRUG INVENTORY AND STORAGE

3M requires its sponsored investigators to maintain adequate drug inventory security at all times. Therefore, the investigator will take the following actions with regard to investigational drugs in concurrence with international regulatory requirements.

1) Upon receipt of clinical trial materials the investigator or designated individual (e.g., a pharmacist) will check the details of the supplies and document receipt.
2) The investigator will keep trial drugs in a pharmacy or a locked and secure storage facility, accessible only to those individuals authorized by the investigator to dispense this investigational drug.
3) The investigator or designated individual will maintain an inventory. This will include the description and quantity of investigational materials received during the course of this trial, as well as a record of the materials that are dispensed and to whom and when these agents are dispensed. This inventory record shall indicate the quantity and description of all investigational materials on hand at any time during the course of the trial.
4) At the conclusion or termination of this trial, the investigator agrees to conduct a final drug supply inventory, to record the results of this inventory and to return all original drug containers, whether empty or containing test preparations, to 3M.
5) The investigator agrees not to supply trial medication to any person except trial personnel and patients in this trial.

11.7 TRIAL MONITORING

3M, as sponsor of this trial, is responsible to regulatory authorities for ensuring the proper conduct of the trial with regards to protocol adherence and validity of the data recorded on the case report forms presented to regulatory authorities. 3M has therefore assigned clinical monitors to this trial. Their duties are to aid the investigator and at the same time, 3M, in the maintenance of complete, legible, well organized, and easily retrievable data. In addition, a monitor will explain, interpret and ensure the investigator's understanding of all applicable regulations concerning the clinical evaluation of a pharmaceutical product (whether licensed or unlicensed) and ensure an understanding of the protocol, reporting responsibilities and the validity of the data.

In order to perform their role well, the 3M monitors must be given access to primary patient data which supports data on the case report forms for the trial, for example, hospital and general practice charts, appointment books, original laboratory records etc. Additionally, a certain amount of judgment must be exercised by the investigator relative to information in a patient's chart which is not relevant to the performance, observations or conduct of this trial. The investigator must make available such records to authorized sponsor, quality assurance and international regulatory personnel for inspection and copying. Because this enters into the realm of patient confidentiality, this fact must be included in the information presented to the patient.

The following is the minimum amount of source data validation (SDV) that will be performed on data from this study:

- 100% SDV on all data up to first dose of study drug
- 100% SDV on all primary efficacy parameters
- 100% SDV on all safety parameters
- 100% SDV on all adverse events and concomitant medications

11.8 3M POLICY ON FRAUD IN CLINICAL TRIALS

In accordance with GCP, it is the sponsor's policy always to follow-up suspected cases of fraud.

11.9 USE OF INFORMATION AND PUBLICATION

It is intended that the results of the trial may be published in the scientific literature. Results may also be used in submissions to regulatory authorities. The following

conditions are to protect commercial confidential materials (patents, etc.), not to restrict publication.

All information concerning imiquimod, 3M operations (such as patent applications, formulae, manufacturing processes, basic scientific data, or formulation information supplied to the investigator by 3M and not previously published) is considered confidential by 3M and shall remain the sole property of 3M. The investigator agrees not to use it for other purposes without 3M written consent.

It is understood by the investigator that 3M will use the information developed in this clinical trial in connection with the development of imiquimod and that it therefore may be disclosed as required to other 3M investigators or any appropriate international regulatory authorities. In order to allow for the use of information derived from this clinical trial, the investigator understands that he/she has an obligation to provide 3M with complete test results and all data developed during this trial.

A manuscript should not be submitted for publication or presentation, until a 3M-sponsored clinical report has been issued, which should be within 12 months of the completion of the clinical phase of the trial. Prior to submitting the results of this trial for publication or presentation, the investigator will allow 3M 30 days in which to review and comment upon the prepublication manuscript. 3M agrees that before it publishes any results of this trial, it shall provide the principal investigator at least 30 days for full review of the prepublication manuscript. The 3M clinical report must be completed and signed off prior to the submission of results for publication. In accordance with generally recognized principles of scientific collaboration, co-authorship with any 3M personnel will be discussed and mutually agreed upon before submission of a manuscript to a publisher. The content of the pre-publication manuscript and the conclusions drawn should be mutually acceptable to both parties before submission to a publisher.

11.10 MODIFICATION OF PROTOCOL

Neither the investigator nor 3M will modify or alter this protocol without first obtaining the concurrence of the other. Approval of the modification by the investigator's IRB must be obtained before implementation, with two exceptions:

1) when necessary to eliminate apparent immediate hazard to the patient, and
2) when the modification does not involve the patient's participation in the trial.

The party initiating an amendment must confirm it clearly in writing and it must be signed and dated by both 3M and the investigator. If necessary, 3M will submit protocol amendments to the appropriate regulatory authorities and notify other investigators using this protocol.

11.11 DEPARTURE FROM PROTOCOL FOR INDIVIDUAL PATIENTS

A "Departure from Protocol" is defined as an emergency, or other circumstance, that requires a decision to be made as to whether the patient (for whom the departure is to be instituted) is to continue in the trial. When the departure occurs, it will be only for that patient. The investigator or other physician in attendance will contact 3M by telephone:

Contact	Office	Home
Assigned Monitor		
Angie Ginkel	1-651-737-2045	1-651-647-9662
Aimee Couture	1-651-733-9670	1-651-714-8120
Mary L. Owens, MD (USA)	1-651-736-3638	1-651-459-0975

The investigator must complete a "Departure from Protocol" form, giving a description of circumstances surrounding the departure, a description of the departure from protocol, name of the 3M individual contacted, reasons for the departure, and the decision of whether or not to continue the patient in the trial. Any minor "Deviations from Protocol" observed for a specific patient, or involving several patients, must be recorded on the appropriate CRF page(s) for each involved patient. "Deviations from Protocol" differ from "Departures from Protocol" by addressing only minor procedure issues that do not affect a patient's adherence to protocol requirements to the extent it could compromise their continued participation in the trial, or the results of the trial.

Examples of protocol deviations that require comment on the CRF, but not a separate departure form, include, but are not limited to the following:

- A single missed visit by a patient (comment to be entered on the first CRF page for the visit.
- A patient visit that is up to 1 week early or late (comment to be entered on the first CRF page for the visit if more than 4 days from scheduled date)
- A post-treatment excisional surgery visit done up to 2 weeks earlier or 2 weeks later than the scheduled 6-week post-treatment date (comment to be entered on the 6-week post-treatment visit CRF page). The excision may only be done early if the treatment site is completely healed, with no evidence of an ongoing inflammatory reaction. All post-treatment excisions must be done at least 4 weeks after treatment ends.
- A dose of drug is removed from the treatment site before 8 hours has elapsed (comment to be entered on dosing record CRF page).

Site personnel should contact the sponsor for any possible departures that are not listed above as deviations, and the sponsor representative will decide whether the circumstance constitutes a "Departure from Protocol" and whether the patient may remain in the trial.

11.12 RECORDS OF TRIAL

In order to comply with international regulatory requirements, the investigator must arrange for the retention of patient identification codes for at least 15 years after the completion or discontinuation of the trial. If applicable, these records must also be retained until 2 years have elapsed following approval by the FDA of a New Drug Application, if this has not been achieved within 15 years of study completion. Patient files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, but not less than 15 years.

Records to be retained by the investigator include, but are not restricted to the following:

1) Investigator's Brochure and updates issued during the clinical conduct of the trial
2) Signed trial protocol, plus all amendments
3) Information given to study patient and any revision during the clinical conduct of the trial:
   - Information Sheet (may be combined with informed consent form)
   - Informed Consent Form (including all applicable translations)
4) Advertisement for patient recruitment (if applicable) and any revision made during the clinical conduct of the trial
5) Clinical trial budget / financial agreement
6) Insurance statement (where required) and any revision during the clinical conduct of the trial
7) Signed agreement between involved parties, e.g.:

- investigator/institution and 3M
- investigator/institution and 3M designee (e.g. contract research organization)
- 3M and designee
- investigator/institution and authority(ies) (where required)
- any revision during the clinical conduct of the trial

8) Dated, documented approval of Independent Ethics Committee (IEC)/Institutional Review Board (IRB) of original:
   - protocol and amendments (if any)
   - CRF (if applicable)
   - Informed Consent Form
   - Patient Information Sheet (if used)
   - Advertisement for patient recruitment (if used)
   - patient compensation where required
   - investigator compensation where required
   - protocol amendments/any revision of the Informed Consent Form/any revision of the Patient Information Sheet/advertisement for patient recruitment (if used) and continuing review of trial (where required)
9) Independent Ethics Committee (EC)/Institutional Review Board (IRB) Composition
10) Regulatory authority authorization/approval/notification of protocol, protocol amendments and other documents (where required)
11) FDA Form 1572, and any update(s)
12) Curriculum vitae of investigator(s) and sub-investigator(s)
13) Normal values for any medical/laboratory/technical procedure or test included in the protocol used to evaluate treatment effects or safety
14) Medical/laboratory/technical/technical procedures/tests (where required):
   - certification or
   - accreditation or

- established quality control and/or external quality assessment or
- other validation

15) Instructions for handling of trial investigational products and trial-related materials (if not included in protocol or Investigator's Brochure)
16) Documentation of shipment of investigational product(s) and trial-related materials
17) Documentation of relevant communications between sponsor and investigative site, other than site visits:
    - letters
    - meeting notes
    - notes of telephone calls
18) Signed, dated Patient Informed Consent Forms
19) Source documents
20) Signed, dated and completed Case Report Forms (CRFs) - yellow copy
21) Documentation of CRF corrections (CRFIs - copy)
22) Notification by originating investigator to 3M of serious adverse events including causality assessments
23) Notification by 3M and/or investigator to regulatory authority(ies) of serious adverse events including causality assessments (where required)
24) Notification by each investigator to the responsible EC/IRB of serious adverse events including causality assessments
25) Interim or annual reports to EC/IRB (where required)
26) Patient Screening Log
27) Patient Identification List (if used)
28) Patient Enrollment Log
29) Investigational product(s) accountability at the site
30) Documentation of investigational product destruction (if destroyed at site)

31) Signature Sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs
32) Records of retained body fluids/tissue samples (if any)

11.13 COMPLETION OF TRIAL

The investigator agrees to complete this trial in compliance with the protocol within 12 months after receipt of trial medication. Continuation of the trial beyond this time must be mutually agreed upon in writing by both the investigator and 3M.

It is agreed that, for reasonable cause, either the investigator or 3M may terminate this trial before the expiration of the agreed time period, provided a written notice is submitted a reasonable time in advance of intended termination.

11.14 TRIAL FUNDING

The costs necessary to perform the trial will be agreed with the investigator and will be documented in a separate financial agreement or investigator contract, which will be signed by 3M and the investigator.

12. REFERENCES

1. Sponsor's Clinical Report Study 1199-IMIQ. Vehicle-Controlled Study Investigating the Mechanism of Action of 5% Imiquimod Cream Applied Three Times a Week for the Treatment of Patients with Genital/Perianal Warts. March 26, 1997. Data on File at 3M Pharmaceuticals.

2. Silverberg E, Boring C, Squires T. Cancer Statistics, 1990. *CA*, 40:18, 1990

3. Miller DL, Weinstock MA. Nonmelanoma Skin Cancer in the United States: incidence. *J Am Acad Dermatol*, 30 (5 Pt 1): 774-8, 1994.

4. McCormack CJ, Kelly JW, Dorevitch AP. Differences in Age and Body Site Distribution of the Histological Subtypes of Basal Cell Carcinoma: A Possible Indication of Differing Causes. *Arch Dermatol*, 133:592, 1997.

5. Silverman MK, Kopf AW, Grin CM, Bart RS, Levenstein MJ. Recurrence Rates of Treated Basal Cell Carcinomas. Part 1: Overview; Part 2: Curettage-Electrodessication. *J Dermatol Surg Oncol*, 1991; 17: 713-718, 720-726.

6. Silverman MK, Kopf AW, Grin CM, Bart RS, Levenstein MJ. Recurrence Rates of Treated Basal Cell Carcinomas. Part 3: Surgical Excision. *J Dermatol Surg Oncol*, 1992; 18: 471-476.

7. Edwards L, Whiting D, Rogers D, Luck K, Smiles KA. The Effect of Intralesional Interferon Gamma on Basal Cell Carcinomas. *J Acad Dermatol*, 22:496, 1990.

8. Preliminary data on file at 3M Pharmaceuticals, St. Paul MN, from ongoing pilot trials 1175-IMIQ and 1236-IMIQ.

9. Full Prescribing Information for Aldara™ (imiquimod) Cream, 5%, March 1997.

10. Edwards L, Ferenczy A, Eron L, Baker D, Owens M, Fox T, Hougham A, Schmitt K, and HPV Study Group. Self-administered Topical 5% Imiquimod Cream for External Anogenital Warts. *Arch Dermatol*, 1998; 134: 23-30.

APPENDIX I

REQUIRED ELEMENTS OF INFORMED CONSENT

[1 of 3 pages]

The Informed Consent must address the following information in simple language, easily understood, and translated when appropriate:

1) Statement that the trial involves research

2) Purpose(s) of the research.

3) Expected duration of participant participation

4) Procedures to be followed and identification of any procedures which are experimental.

5) Reasonable foreseeable risks or discomforts to the participant.

- Risks/discomfort from trial procedures
- Foreseeable risks associated with trial drug which includes adverse events listed in the Investigator's Brochure or package insert

6) Benefits to the participant or to others which may reasonably be expected from the research, including amount and stipulation of monetary compensation.

7) Appropriate alternative procedures or courses of treatment, if any, that may be advantageous to the participant.

8) Extent to which the confidentiality of records identifying the patient will be maintained; including the possibility that representatives of 3M Pharmaceuticals, the FDA and the TGA may inspect the records.

9) Compensation and medical treatment available if injury occurs. The following wording is required: "3M Pharmaceuticals will pay medical expenses due to any medical problems caused by [trial drug] as specified in the protocol. However, one of the risks that you assume by participating in this trial is the possibility that [trial drug] will not be effective for you and will not treat or improve the condition for which you have sought treatment. If you suffer any medical problems from the failure of [trial drug] to effectively treat or improve your condition, 3M Pharmaceuticals will not pay your medical expenses unless another successful treatment was specifically discontinued for this trial."

10) Whom to contact for answers to pertinent questions about the research and research participant's rights.

11) Whom to contact in the event of research-related injury to the participant.

APPENDIX I:
REQUIRED ELEMENTS OF INFORMED CONSENT

[page 2 of 3]

12) Participation is voluntary, i.e.:
- Refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled.
- Participant may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled.

Additional Elements Of Informed Consent

When appropriate, one or more of the following elements of information should also be provided to each participant:

1) Particular treatment or procedure may involve risks to the participant (or to the embryo or fetus, if the patient may become pregnant) which are currently unforeseeable.
2) Anticipated circumstances under which the participant's participation may be terminated by the investigator without regard to the participant's consent.
3) Any additional costs to the participant that may result from participation in the research.
4) Consequences of participant's decision t withdraw and procedures for orderly termination by patient.
5) Significant new findings developed during the course of the research which may relate to the participant's willingness to continue participation will be provided to the participant.
6) Approximate number of participants involved in the trial.

Special Considerations for Informed Consent

An addendum to the informed consent for women of childbearing potential.

APPENDIX I

ATTACHMENT A, ADDENDUM TO CONSENT FORM FOR WOMEN OF CHILDBEARING POTENTIAL

[3 of 3 pages]

Protocol Title: A 12-Week Dose Optimization Trial Evaluating 5% Imiquimod and Vehicle Cream for the Treatment of Superficial Basal Carcinoma

Protocol Number: 1305-IMIQ

To the best of my knowledge, I am menstruating normally, I have no reason to believe I am pregnant and I am practicing a medically acceptable method of birth control such as oral contraceptives, an IUD (coil) or complete abstinence from sexual intercourse. I have been told that a woman who believes she is pregnant, is thinking about becoming pregnant or has not used acceptable birth control in the past six to eight weeks should NOT participate in this trial.

The investigator has explained to me that the effect of the drug on a unborn child is not fully known. I have also been told of a potential danger any drug has on an unborn child. It is not fully known if this drug can be absorbed from the skin. Animal studies have shown decreased fetal body weight and reversible delays in bone formation at high levels of this drug.

I have been told and understand that is it very important that I carefully and completely give the investigator my menstrual and birth control history. Although a pregnancy test will be done before beginning the drug, I have been informed by the investigator that this test may, in some circumstances, provide false negative results saying that I am not pregnant, while I actually am pregnant.

If I have any questions about the possibility of pregnancy, either now or at any time during the trial, I will immediately ask the investigator. If I think I may be pregnant at any time during the trial, I will immediately notify the investigator.

I have read and understand this section of the consent form.

_____ _____

Participant Signature Date
(or legal representative - indicate relationship to participant)

_____

Printed Participant Name

_____ _____

Witness Signature Date

_____ _____

Printed Witness Name Date

APPENDIX II
PATIENT GUIDELINES FOR APPLICATION AND REMOVAL OF IMIQUIMOD CREAM

1) Keep the packets of imiquimod cream at room temperature. Avoid temperatures greater than 25°C (77°F). Avoid Freezing.

2) Wash your hands and the tumor area with mild soap and water. Dry your hands and the tumor area thoroughly.

3) Gently squeeze the amount of cream you have been instructed to use out of the packet onto your fingertip.

4) Gently rub the cream on the tumor area and about 1/4 inch (1 cm) around it until the cream disappears.

5) Put the opened, used packet in the self-sealing bag labeled for used packets. You should take all packets (opened and unopened) to your next clinic visit (except "Emergency Use" kits).

6) After you have finished applying the cream, wash your hands with mild soap and water.

7) The study nurse or doctor will tell you how often to apply the cream. The cream should stay on your skin for at least 8 hours before you wash the area.

8) Each time you apply or remove study cream (by washing), record the date and time of the removal of the previous dose and the application of a new dose.

9) If you take any other drugs during this study, you should tell the study nurse or doctor. They will need to know the name of the drug, how much you took, how often you took it and why you took it.

10) Some drugs are not allowed at all during the study. The study nurse or doctor will discuss these drugs with you. If you have any questions about whether or not you can take a certain drug, please contact the study nurse.

1. TITLE PAGE

Title: A 12-Week Dose Response Study Evaluating Imiquimod 5% and Vehicle Cream for the Treatment of Superficial Basal Cell Carcinoma

Sponsor: 3M Pharmaceuticals

Protocol ID: 1305-IMIQ

Phase: II

First Patient Initiated: 22 July 1998

Last Patient Completed: 19 January 2000

Conduct Statement: This study was conducted in compliance with the Code of Federal Regulations of the United States Food and Drug Administrations (FDA), 21 CRF Part 56, Institution Review Boards and 21 CRF Part 50, Protection of Human Subjects, and the ethical principles enunciated in the revised Declaration of Helsinki (Somerset West, Republic of South Africa, October 1996).

Principal Investigator: John K. Geisse, MD,
Solano Dermatology Associates
127 Hospital Dr. Suite 204
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Telephone: (707) 643-5785

Sponsor Signatory: Herbert B. Slade, MD
Director, US and International
Medical Affairs
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2. SYNOPSIS

[page 1 of 4]

Name of Sponsor: 3M Pharmaceuticals	**Individual Study Table Referring to Dossier Part Volume:**	*(For National Authority Use Only)*
Name of Finished Product: Aldara™		
Name of Active Ingredient: Imiquimod (R-837)	**Report:**	

Study Title: A 12-Week Dose Response Study Evaluating Imiquimod 5% and Vehicle Cream for the Treatment of Superficial Basal Cell Carcinoma.

Investigator(s):

Principal Investigator: John K. Geisse, M.D., Solano Dermatology Associates., Vallejo, Calif

- Libby Edwards, M.D., Carolinas Medical Center, Charlotte, NC
- Rokea A. el-Azhary, M.D., Mayo Clinic, Rochester, Minn
- Robert E. Clark, M.D., Duke University Medical Center, Durham, NC
- Hubert T. Greenway, M.D., Scripps Clinic, La Jolla, Calif
- Norman Levine, M.D., University of Arizona, Tucson, Ariz
- Ida Orengo, M.D., Baylor College of Medicine, Houston, Tex
- Phoebe Rich, M.D., Northwest Cutaneous Research Specialists, Portland, Ore
- June K. Robinson, M.D., Loyola University Medical Center Maywood, Ill
- Amit Pandya, M.D., UT Southwestern Medical Center, Dallas, Tex
- Kenneth Gross, M.D., Skin Surgery Medical Group, Inc., San Diego, Calif
- James Swinehart, M.D., Colorado Medical Research Center, Denver, Colo
- David Tashjian, M.D., Central California Medical Research, Fresno, Calif
- Stephen Tyring, M.D., University of Texas, Galveston, Tex
- Elizabeth Shurnas & Paul Brownstone, M.D., Alpine Clinical Research Center, Boulder, Colo

Study Center(s): 15 centers in the United States (13 centers enrolled patients)

Publication (reference): None.

Study Period: (first patient initiated)	22 July 1998	**Phase of Development:** II
(last patient completed)	19 January 2000	

Objective: The objective of this study was to establish a safe and efficacious treatment regimen using topical imiquimod 5% cream for the treatment of superficial basal cell carcinoma (sBCC).

Methodology: This was a phase II, randomized, double-blind, vehicle-controlled multicenter dose response study conducted in the United States. The study consisted of a pretreatment screening visit, a 12-week treatment period with regularly scheduled interval visits, and a 6-week posttreatment visit for surgical excision of the target tumor area. The screening visit was held 2 to 4 weeks prior to initiation, at which time patients who met the inclusion and exclusion criteria were informed of study procedures and of their rights and responsibilities as study participants. Before study-specific procedures were begun, patients signed a written informed consent. A biopsy consisting of no more than 25% of the tumor area was taken for histologic confirmation of sBCC. The randomization schedule in the original protocol assigned patients at random to either imiquimod or vehicle in 1 of 3 dosing regimens: once daily 3 days per week, once daily 7 days per week, or twice daily 7 days per week. The block size used was 12 patients. For each dosing regimen, an unequal randomization of 3:1 imiquimod:vehicle was used. During the 12-week treatment period, patients were to return to the clinic at the end of weeks 1, 2, 4, 6, 8, and 10. At these clinic visits, the target tumor was photographed, and each patient was monitored for treatment compliance, local skin reactions (LSRs), adverse events (AEs), and concomitant medications use. The tumor was measured at initiation and, if clinically evident, before excision. Six weeks after the treatment period, patients were to return to the clinic to undergo surgical excision of the target tumor area. The tissue was examined for histologic evidence of residual BCC and to ensure that the tissue margins were free of tumor.

2. SYNOPSIS

[page 2 of 4]

Name of Sponsor: 3M Pharmaceuticals	**Individual Study Table Referring to Dossier Part Volume:**	*(For National Authority Use Only)*
Name of Finished Product: Aldara		
Name of Active Ingredient: Imiquimod (R-837)	**Report:**	

Methodology (cont'd): The protocol was modified by 2 amendments, 1 Note to File (NTF) and 1 administrative revision. Amendment I was incorporated prior to the enrollment of patients and clarified biopsy and excision procedures. Amendment II allowed for replacement of the twice daily 7 days per week regimen with the once daily 5 days per week regimen and discontinuation of patients who required more than 2 rest periods (for a combined total of 14 days). The NTF (No. 2) allowed for up to 4 prestudy biopsies. Both amendments and the NTF were submitted to and received approval from the designated institutional review boards (IRBs). Included in the 5 items addressed in the administrative revision, the word Optimization in the title was changed to Response to more accurately describe the study. In addition, the revision stated that if nodular and superficial components were present in the target tumor, the tumor would be classified as nodular and not eligible for treatment in this study.

Number of Patients: One hundred twenty-eight (128) patients, including 82 males and 46 females were enrolled and randomized to treatment. The mean age was 59 years. All patients were white with Fitzpatrick skin types I-IV: 46% had skin type II (tans minimally), and 34% had skin type III (tans gradually).

Diagnosis and Main Criteria for Inclusion: Patients eligible for this study were males or females 18 years of age or older who met the inclusion/exclusion criteria and had a histologically confirmed diagnosis of sBCC. The target tumor was to be located on the head, trunk, or limbs (excluded sites were areas within 1.0 cm of hairline, eyes, nose, mouth, or ears; the anogenital area; and hands and feet). The tumor was to be primary (not recurrent or previously treated), noninfected, and measure 0.5 cm^2 to 2.0 cm^2.

Test Product, Dose, and Mode of Administration, Batch Number: Imiquimod 5% topical cream (formulation U-2e) administered topically from single-use packets. Each packet contained 250 mg of cream (12.5 mg imiquimod). Lot numbers PD-10073 and 98L02B. Mean cumulative dose of imiquimod (range for the 4 dosing groups) approximately 43 to 146 mg.

Duration of Treatment: Twelve weeks of treatment with study drug, followed by a 6-week posttreatment surgical excision of the target tumor area and excision follow-up.

Reference Therapy, Dose and Mode of Administration, Batch Number: Topical vehicle cream, lot numbers GS3965A and ME4183A.

Criteria for Evaluation:

Efficacy The primary variable was the complete response rate, defined as the proportion of patients who had no histologic evidence of BCC in the excised posttreatment target tumor tissue.

Safety Adverse events (AEs), local skin reactions (LSRs), laboratory data, vital signs, physical examinations, and concomitant and prestudy medications were measured and analyzed for safety.

Statistical Methods: Three data sets were analyzed: intent-to-treat (ITT), consisting of all randomized patients; ITT-Superficial (ITT-S), consisting of all patients with histologically confirmed diagnosis of sBCC; and per-protocol (PP), consisting of ITT-S patients who were free from major protocol violations, who underwent posttreatment surgical excision of the target tumor area, and who applied at least 60% of the doses required by the dosing regimen. Complete response rate was plotted vs dosing frequency per week to visually examine the shape of the dose-response curve. Tests for trend and model fitting were done to further characterize the dose-response function. Therapeutic window plots of complete response rate and severe scabbing rate at each dose level were used to estimate the benefit-to-risk ratios. All safety data were tabulated separately by treatment group, using the ITT data set.

2. SYNOPSIS

[page 3 of 4]

Name of Sponsor: 3M Pharmaceuticals	**Individual Study Table Referring to Dossier Part Volume:**	*(For National Authority Use Only)*
Name of Finished Product: Aldara		
Name of Active Ingredient: Imiquimod (R-837)	**Report:**	

Summary - Conclusions: **Efficacy Results:** Greater than 50% of patients in all imiquimod dose groups experienced complete clearance of BCC in the target tumor tissue excised 6 weeks following treatment. Increasing rates of clearance were observed with increasing frequency of dosing:

Dose Group (n)	Number of Patients Cleared (ITT-Data Set)
Twice daily 7 days per week (10)	10 (100%)
Once daily 7 days per week (31)	27 (87.1%)
Once daily 5 days per week (26)	21 (80.8%)
Once daily 3 days per week (29)	15 (51.7%)
Combined vehicle (32)	6 (18.8%)

Safety Results: Every treatment group had at least 1 patient-reported AE, with application site reactions reported most often:

Dose Group (n)	No. of Patients with Application Site Reactions (ITT Data Set)
Twice daily 7 days per week (10)	8 (80%)
Once daily 7 days per week (31)	25 (80.6%)
Once daily 5 days per week (26)	20 (76.9%)
Once daily 3 days per week (29)	16 (55.2%)
Combined vehicle (32)	8 (25.0%)

Twenty-five patients reported at least 1 severe AE, including 5 patients with application site reactions that were considered probably or possibly related to study drug. Four patients discontinued the study due to application site reactions. Five patients reported 6 serious AEs, none related to study drug.

Patients in all dose groups reported LSRs. The severity of LSRs increased as dosing frequency increased. The twice daily 7 days per week regimen was discontinued due to the frequency and severity of LSRs and application site reactions. Thirteen patients discontinued from the study due to LSRs, but overall, the incidence of severe reactions was low. No severe scabbing was observed in the combined vehicle group.

Imiquimod Dose Group (n)	No. of Patients with Severe Scabbing (ITT Data Set)
Twice daily 7 days per week (10)	3 (30.0%)
Once daily 7 days per week (31)	9 (29.0%)
Once daily 5 days per week (26)	2 (7.7%)
Once daily 3 days per week (29)	2 (6.9%)
Combined Vehicle (32)	0 (0%)

2. SYNOPSIS

[page 4 of 4]

Name of Sponsor: 3M Pharmaceuticals	**Individual Study Table Referring to Dossier Part Volume:**	*(For National Authority Use Only)*
Name of Finished Product: Aldara		
Name of Active Ingredient: Imiquimod (R-837)	**Report:**	

Of 128 patients, 13 (10.2%) discontinued due to LSRs, 4 (3.1%) discontinued due to AEs, 2 (1.6%) discontinued due to noncompliance, 2 (1.6%) discontinued for personal reasons, 2 (1.6%) were lost to follow-up, and 1 (0.8%) was discontinued for a laboratory abnormality. No clinically meaningful changes from baseline in laboratory values, physical examinations, or vital sign measurements were noted. Medical histories and concomitant medications were typical for this age group. No pregnancies were reported. There were no deaths in this study.

CONCLUSIONS: Imiquimod 5% cream was effective in the treatment of sBCC in all dosing regimens used in this study. The complete response rate increased as dosing frequency increased. Imiquimod 5% cream exhibited a more acceptable patient safety profile when used at dosing frequencies less often than twice daily 7 days per week. The once daily 5 or 7 days per week dose groups had the highest efficacy results with acceptable safety profiles.

Date of Report: 29 November 2000

3M PHARMACEUTICALS

Study 1305-IMIQ

IMIQ-TP-XX-CM-97-US-M

Final Report – 29 November 2000

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